DISSERTATION ON

RISK FACTORS FOR HEPATOTOXICITY FOLLOWING HAART IN HIV PATIENTS

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CERTIFICATE

This is to certify that the dissertation entitled **"RISK FACTORS FOR HEPATOTOXICITY FOLLOWING HAART IN HIV PATIENTS"**submitted by **Dr.A.T.MAASILA,** appearing for Part II M.D. Branch I General Medicine Degree Examination in April 2011, is a bonafide record of work done by him under my direct guidance and supervision in partial fulfilment of regulations of the Tamil Nadu Dr. M.G.R. Medical University, Chennai. I forward this to the Tamil Nadu Dr.M.G.R. Medical University, Chennai, Tamil Nadu, India.

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I solemnly declare that the dissertation titled **" RISK FACTORS FOR HEPATOTOXICITY FOLLOWING HAART IN HIV PATIENTS"** is done by me at Tirunelveli Medical College hospital, Tirunelveli under the guidance and supervision of **Associate Professor, Dr.Arumugapandian @ Mohan M.D**.,

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This is to certify that the INSTITUTIONAL ETHICAL COMMITTEE of TIRUNELVELI MEDICAL COLLEGE AND HOSPITAL, TIRUNELVELI-11 has unanimously approved the dissertation titled RISK FACTORS FOR HEPATOTOXICITY FOLLOWING HAART THERAPY IN HIV PATIENTS by DR.A.T.MASILA,MD (GM) II YEAR student, TIRUNELVELI MEDICAL COLLEGE, TIRUNELVELI-11 in its meeting held on 09.10.2009.

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LIST OF ABBREVIATIONS USED

ACTG	AIDS Clinical Trials Group
AIDS	Acquired immunodeficiency syndrome
ALT	Alanine aminotransferase
APV	Amprenavir
ARLI	Antiretroviral drug-related liver injury
ART	Antiretroviral therapy
AST	Aspartate aminotransferase
ATV	Atazanavir
AZT	Zidovudine (also known as ZDV)
BMI	Body Mass Index
CCR5	Chemokine receptor 5
CD4	Cluster differentiation
CMV	Cytomegalovirus
CT	Computed Tomography
CTX	Co-Trimoxazole
d4T	Stavudine
ddC	Zalcitabine
ddI	Didanosine
DNA	Deoxyribonucleic acid
EBV	Epstein-Barr virus
EFV	Efavirenz

ERCP	Endoscopic Retrograde Cholangio Pancreatography
FDA	Food & Drug Administration
FTC	Emtricitabine
GBV-C	Hepatitis G Virus
HAART	Highly Active Anti-Retroviral Therapy
HAV	Hepatitis A Virus
HBsAg	Hepatitis B Surface Antigen
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HDV	Hepatitis D Virus
HSV	Herpes Simplex Virus
HHV-8	Human Herpes Virus 8
HIV	Human Immunodeficiency Virus
IDV	Indinavir
IFN	Interferon
INH	isoniazid
LPV	lopinavir
MAC	Mycobacterium Avium Complex
MTB	Mycobacterium Tuberculosis
NNRTI	Non-Nucleoside Reverse Transcriptase Inhibitor
NRTI	Nucleoside Reverse Transcriptase Inhibitor
NFV	Nelfinavir

NVP	Nevirapine
OI	Opportunistic Infections
PI	Protease Inhibitor
RNA	Ribonucleic Acid
RTV	Ritonavir
SMX	Sulfamethaoxzole
SQV	Saquinavir
3TC	lamivudine
T20	Enfuvirtide
TMP	Trimethoprim
TDF	Tenofovir
TPV	Tipranavir
ULN	Upper Limit of Normal
VZV	Varicella zoster virus

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Introduction

INTRODUCTION

Human immunodeficiency virus (HIV) infection/Acquired Immunodeficiency Syndrome is a global pandemic, with cases reported from virtually every country. With more than 35 million fatalities, the AIDS epidemic now ranks alongside the influenza pandemic of the early 1900s and the Bubonic plague of the fourteenth century in terms of fatalities.[1]

Statistics for the end of 2008 indicate that around 33 million people are living with HIV, the virus that causes AIDS. Each year around 2.7 million more people become infected with HIV and 2 million die of AIDS.[2]Although HIV and AIDS are found in all parts of the world, the worst affected region is sub-Saharan Africa, where in a few countries more than one in five adults are infected with HIV. The epidemic is spreading most rapidly in Eastern Europe and Central Asia, where the number of people living with HIV increased to 67% between 2001 and 2008.

Gastroenterological manifestations are quite common in advanced HIV infection/ AIDS and are sometimes the initial manifestations or AIDS defining illness. Liver involvement is unique since it can be because of direct involvement, opportunistic infections (OI) with co-infection of one or more hepatotoxic viruses, or because of toxicity due to antiretroviral drugs.[3]

HEPATOBILIARY MANIFESTAIONS OF HIV/AIDS:

Liver disease has assumed a far greater importance as a cause of morbidity and mortality in patients infected with human immunodeficiency virus (HIV) because of their increased life expectancy as a result of antiretroviral therapy (ART). Presence of liver disease is a frequent finding in AIDS. Hepatomegaly may be detected on examination in most patients. Hepatomegaly is usually associated with one or more biochemical test abnormalities, although significant jaundice due to parenchymal disease is uncommon.

As with other organ systems, the spectrum of hepatic infections in patients with HIV evolves as immunocompromise advances. Hepatobiliary disease in HIV-infected patients can be divided into two groups: Those with severe immunosuppression, who commonly have opportunistic infections, and those with suppressed HIV viral loads and minimal immunosuppression. Clinical manifestations of hepatobiliary disease can vary from no symptoms to liver failure.

Table 1.1 - MAJOR CAUSES OF LIVER INJURY IN HIV-INFECTED PATIENTS

DRUGS
ART: NRTI, NNRTI, PI Antimicrobial agents: Antituberculosis (INH, rifampin) Macrolides (clarithromycin, azithromycin) Antifungal (ketoconazole, itraconazole, fluconazole) Antipneumocystis (TMP-SMX, pentamidine, dapsone)
INFECTIONS
Viral (HAV, HBV, HCV, HDV, GBV-C, CMV, HSV, VZV, EBV) Mycobacterial (Mycobacterium avium, Mycobacterium tuberculosis, other Mycobacteria)
Fungal (cryptococcus, histoplasma, coccidioides, candida) Protozoan (pneumocystis, toxoplasma, microsporidia, cryptosporidium)
BILIARY TRACT INFECTIONS
HIV cholangiopathy, Acalculous cholecystitis
NEOPLASMS AND VASCULAR LESIONS
Kaposi sarcoma, Lymphoma, Peliosis hepatitis
STEATOSIS WITH LIPODYSTROPHY
HCV/HIV coinfection Drug-associated (PI and NRTI).

DRUGS:

Drug-induced liver injury has emerged as the most prevalent cause of liver test abnormalities and is related to the increasing array of antiretroviral medications. Use of prescription or non-prescription drugs as well as herbal remedies should also be considered a cause of abnormal liver test results in the HIV-infected patient. Before HAART, drug hepatotoxicity was most commonly due to sulfonamides, and the increased frequency of adverse reactions to these medications is well recognized in AIDS.

The lactic acidosis syndrome, characterized by marked hepatomegaly, steatosis, metabolic lactic acidosis, and liver failure, is now well recognized. The liver tests typically show a hepatocellular pattern but can be normal or minimally increased. Hepatic steatosis is evident on imaging of the liver. Although reversal has occurred in some patients following drug withdrawal, most patients have worsening disease and death. Liver transplantation is curative.

The incidence of drug induced hepatotoxicity, its mechanisms, evaluation, management, analyses of various studies on the risk factors and prognosis are described in detail in Literature review.

INFECTIONS:

Viral Infections, of the liver are often because of herpes viridae family. *CMV* is detected frequently in autopsies of severely immunosuppressed patients with CD4 counts less than 100/mm^3 and is often

a component of systemic involvement .CMV infects every type of cell within the liver. CMV infection is being detected earlier now owing to pp65 antigen flow cytometry and CMV polymerase chain reaction.

Hepatitis secondary to *HSV* occurs in patients with extensive herpetic ulcers elsewhere. Pathologically, HSV hepatitis is characterized by multinucleated hepatocytes and Cowdry type A intranuclear inclusion bodies that may be differentiated from those of CMV by specific immuno-histochemistry. *Varicella-zoster virus, EBV, and adenovirus* are the other agents responsible for viral hepatitis in patients with HIV.

Clinical manifestations and histologic features of viral hepatitis from HBV, HCV, or hepatitis D virus are altered in the presence of HIV coinfection but in remarkably different ways for each virus. Because of common epidemiologic risks of transmission including sexual and parenteral exposures, coinfection of hepatitis B virus (HBV) with HIV is common. Decreased response to HIV-ART and a higher risk of hepatic decompensation was observed in HBV/HIV-coinfected patients compared with those of HIV monoinfected patients. [4] Clinical and autopsy studies in AIDS patients have reported up to a 90% sera prevalence of hepatitis B markers indicating past or present infection.

Concurrent HIV and **HBV** infections lead to alterations of HBV antigen-antibody display, viral replication, and clinical consequences. Several reports have described reappearance of hepatitis B surface antigen

(Bag) in HIV-infected patients previously thought to be immune to hepatitis B virus as indicated by the presence of anti-HBs.[4]Recurrence of Bag may arise from either reinfection or reactivation with advanced immunodeficiency. In addition, there is an accelerated loss of naturally acquired anti-HBs even in those patients who remain HBsAg negative. With loss or reduction in immunity to HBV, there is an increased prevalence of hepatitis B e antigen expression, elevated mean levels of DNA polymerase, and increased titers of anti–hepatitis B core antigen.[5]

Acquisition of the chronic carrier state is also much more likely in the HIV-infected patient, especially if infection occurs when immunodeficiency is more advanced. Thus, a larger proportion of patients with HIV and hepatitis B infections have a chronic carrier state, with highly infectious serum and body fluids, compared with those who are HIV negative. Although HIV infection leads to more prevalent chronic HBV carriage, it appears to attenuate the severity of biochemical and histologic liver disease in most, but not all patients.

In one study, the mean alanine aminotransferase (ALT) level correlated with CD4 lymphocyte count. The mechanism for reduced hepatitis B virus–related liver injury following HIV infection is not certain but has been attributed to a diminution in lymphocyte-mediated hepatocellular injury as a result of HIV effects on lymphocytes. In those patients without serologic evidence of past or present hepatitis B virus and

HIV infection, vaccination appears to be ineffective, regardless of the stage of immuno compromise. Sometimes the institution of HAART in a chronic carrier of hepatitis B virus can have catastrophic consequences. Patients may develop an acute flare of hepatitis that can be severe leading to fulminant hepatic failure. However, the proportion of coinfected patients who develop an acute hepatitis B flare following use of HAART is unknown. It is believed that reconstitution of immune function with HAART leads to production of antibody that is directed to infected hepatocytes as in the normal host. Inclusion of lamivudine, which has potent antiviral effects on hepatitis B virus, in the HAART regimen may reduce the likelihood of acute hepatitis B.[5]The consequences of HIV infection on **delta hepatitis** appear similar to those of HBV, although far fewer patients have been studied.

The prevalence of **HCV** in those with HIV infection depends on the risk group evaluated and the assay used. Prevalence is highest in injection drug users (52% to 89%)[6] and hemophiliac patients with HIV, whereas in military populations and non–drug users, the prevalence is much lower, ranging from 1% to 11%. Assaying antibodies to hepatitis C virus alone, rather than hepatitis C virus RNA, may underestimate the true prevalence, because loss of antibody may occur with progression of immunodeficiency.[4],[5]Unlike hepatitis B virus, the clinical course of hepatitis C virus appears to worsen as HIV-related immune compromise

advances. This has been best documented in HIV infected hemophiliac patients. Studies in large cohorts of hemophiliac patients have demonstrated dramatic increases in hepatitis C virus RNA levels with progressive HIV disease, associated with aspartate aminotransferase (AST) elevations and hepatomegaly. Coinfected patients also have a higher rate of active cirrhosis on biopsy and an accelerated course to clinical cirrhosis and liver failure.

Factors that predict fibrosis and progression to cirrhosis in coinfected patients include: older age at infection, higher alanine aminotransferase levels, higher inflammatory activity, alcohol consumption of more than 50 g/day and CD4+ T cell count of less than 500 cells/mm.[3],[7],[8]The mechanism for this more rapid disease course is unknown but has been similarly recognized in other immunocompromised patients. Because patients with late-stage HIV often have multiple life- threatening infections, HCV alone is not an independent determinant of mortality.

However, as HIV-infected patients are living longer owing to HAART, hepatitis C virus–induced liver disease and its consequences (e.g., hepatocellular cancer) are assuming more clinical relevance. Like hepatitis B, hepatitis C virus does not cause progression of HIV disease.[6]The effect of HAART on hepatitis C viral dynamics and liver injury is variable. Some studies have found attenuation of disease, whereas others had documented exacerbations reflected by increases in serum transaminases. Hepatitis C viral load has also been variably affected.[9]The role of interferon therapy for

HIV/HCV coinfected patients remains unsettled. α-Interferon is less effective for treating hepatitis C virus liver disease in coinfected patients. More recently, combination therapy of Peg-interferon and ribavirin has shown promise.[10]

Mycobacterial Infections, most common opportunistic pathogen affecting the liver. Infection with MAC manifests with systemic symptoms and signs, such as fever, abdominal pain, wasting, and biliary obstruction secondary to enlarged lymph nodes at the porta hepatis. It is ordinarily seen in late stage AIDS patients with CD4 count less than 50 cells/mm^3. MAC is detected in 20% to 55% of autopsies and in 10% to 30% of liver biopsies in patients with AIDS. Blood cultures are the most sensitive test for diagnosis of MAC. On the other hand, liver biopsy showing diffuse, poorly formed noncaseating granulomas is necessary for definitive diagnosis of liver involvement. Liver tissue culture is needed to distinguish between different Mycobacterium species. Liver biopsy has been reported to be more sensitive than bone marrow biopsy in diagnosing disseminated mycobacterial infection in AIDS.[11]Extrapulmonary *Mycobacterium tuberculosis (MTB)* infection involving the liver occurs in 5% to 10% of HIV-related tuberculosis cases and may present with tuberculous liver abscess in severely immune compromised patients.[12]As the virulence of MTB is greater than in the other species of Mycobacterium, it may infect the patients who have higher CD4 counts, more than 200/mm^3.[13]The specific

diagnosis is made by culture and polymerase chain reaction of blood, urine or tissue specimen including liver. Acid-fast bacilli may be seen in the liver histology, which is typically characterized by presence of caseating granulomas. Rarely, liver infections with other mycobacterial species such as *Mycobacterium kansasii, Mycobacterium xenopi*, and *Mycobacterium genavense* have also been reported.

Fungal Infections infecting the liver are Cryptococcus neoformans, Histoplasma capsulatum, Coccidioides immitis and Candida albicans. They are uncommon and ordinarily seen in the setting of disseminated disease, in patients with less than 100 CD4 cells/mm^3. Liver histology often reveals poorly formed granulomas with minimal inflammatory reaction.

Meningitis is the most common manifestation of cryptococcal disease in HIV-infected patients. Liver involvement occurs because of haematogenous spread. The common presenting features are fever and hepatosplenomegaly. Progressive disseminated histoplasmosisis often the first sign of immunodeficiency in patients with AIDS in endemic areas.[14] Constitutional symptoms along with hepatosplenomegaly and lymphadenopathy are the common features.

C. immitis infection presents with pulmonary involvement, hepatic infection is again secondary to disseminated disease. Systemic infection and liver involvement with candidiasis are quite rare unless the patients are neutropenic. The symptoms are nonspecific such as nausea, vomiting,

abdominal pain, and hepatomegaly. C. neoformans and H. capsulatum may be rapidly detected by polysaccharide capsular antigenemia; There are also rare reports of Aspergillus fumigatus causing liver abscess and disseminated Sporothrix schenckii involving the liver. .

Protozoa, are rare pathogens causing infections in patients with AIDS. The routine prophylaxis with trimethoprim/sulfamethoxazole (TMP-SMX) has reduced the incidence of Pneumocystis jirovecii, Toxoplasma gondii, and Listeria monocytogenes. In the past P. jirovecii (formerly Pneumocystis carinii) hepatitis was associated with the prophylactic use of aerosolized pentamidine for pneumocystis pneumonia.[15],[16] Inhalation failed to provide adequate drug levels to extra pulmonary sites and up to 39% of such patients developed extrapulmonary spread.[17] Abdominal CT scan may demonstrate diffuse and punctate calcifications in the liver. Liver biopsy shows foamy nodules that are periportal or diffuse containing numerous Pneumocystis cysts that stain with Gomori's methenamine-silver.

T.gondii also involves the liver rarely through haematogenous dissemination and may present with granulomatous disease or hepatitis. Diagnosis is made by culture or microscopic examination of Giemsa-stained specimens. Microsporidial infection of the liver is rare. Light microscopy reveals focal granulomatous and suppurative necrosis, mainly in the portal area, accompanied by characteristic spores.

Strongyloides stercoralis, a helminth of the nematode family, may result in a hyperinfection syndrome in the immuno compromised patient. The liver is

involved through the haematogenous spread of the larvae from the gastrointestinal tract. Entamoeba histolytica may invade the bowel wall and spread to the liver, forming an abscess. Reactivated Leishmania donovani is another rare infection of the liver .The biliary tree including the gall bladder, is a common site of infection in HIV infected patients with immunosuppression. It may be involved in the form of acalculous cholecystitis or cholangiopathy.

Hepatic microabscesses or macroabscesses are most likely to occur if the patient is neutropenic, especially following chemotherapy for non-Hodgkin's lymphoma. Kaposi's sarcoma, which is caused by infection with human herpesvirus 8 (HHV-8) has a predilection for periportal regions of the liver and is seen in 10% to 15% of liver biopsies. Tumor nodules appear grossly as violaceous or hemorrhagic masses within hepatic parenchyma. Microscopically, the characteristic spindle cells and vascular slits of Kaposi's sarcoma usually directly abut normal-appearing liver tissue. Hepatic involvement by non-Hodgkin's lymphoma may be the index manifestation of AIDS in homosexual men and may be the primary site of the neoplasm. The lesions are usually focal and may be large. In addition, Hodgkin's disease in the AIDS patient tends to be more aggressive histologically and clinically, spreading rapidly to extranodal sites making liver involvement more likely. Bacillary peliosis hepatitis may be caused by either Bartonella henselae or Bartonella quintana.

Biliary tract involvement in AIDS may result in marked liver test abnormalities and right upper quadrant symptoms, jaundice is unusual. A syndrome resembling sclerosing cholangitis with papillary stenosis is well recognized and has been termed *AIDS cholangiopathy*. Patients characteristically develop significant upper abdominal pain in association with marked elevation of alkaline phosphatase, and minimal elevations of bilirubin, AST, and ALT.

Other less common causes of biliary tract disease in AIDS include primary bile duct lymphoma, epithelial angiomatosis, lymphomatous nodal obstruction, Kaposi's sarcoma, and biloma. In addition, chronic pancreatitis or choledocholithiasis may lead to biliary obstruction, although their incidence is not clearly increased in HIV infection.[3][4]

EVALUATION:

The initial decision in evaluating the AIDS patient with jaundice, hepatomegaly, or both, is to determine whether the findings are due to intrahepatic or extrahepatic disease. Simultaneous disease in both sites must also be considered. A history of mild jaundice, often in association with fever and constitutional symptoms, is more consistent with intrahepatic disease, whereas symptoms of deep jaundice associated with pain of relatively acute onset suggest extrahepatic disease.

Careful review of medications, both prescription and non-prescription, is essential. Because the clinical history and the finding of symptomatic hepatomegaly are nonspecific, further evaluation is always

necessary. Elevations of ALT or AST or both are common, but neither the pattern nor the extent of elevation of these tests appears to correlate with specific findings in the liver. Significant elevation of the transaminases favours a drug-induced or viral cause. In contrast, marked elevation of alkaline phosphatase correlates statistically with the presence of MAC infection in the liver in AIDS when extrahepatic obstruction is absent.

The indications for liver biopsy for the patient in whom intrahepatic disease is suspected are not well defined. Biopsy is appropriate when symptomatic, treatable disease of the liver is suspected and when a specific diagnosis of hepatic disease is needed. An extrahepatic cause for jaundice is suggested on CT or ultrasonography by the presence of dilated ducts or other biliary and/or pancreatic abnormalities. Once extrahepatic obstruction is recognized, the possibility of papillary stenosis associated with AIDS cholangiopathy must be considered as well as the possibility of choledocholithiasis or other disorders, depending on the imaging studies. Further evaluation, when indicated, may include endoscopic retrograde cholangiopancreatography (ERCP) if CT or ultrasonography demonstrates extrahepatic biliary ductal dilatation. Ampullary and duodenal biopsy specimens or bile and/or biliary cytology (with appropriate staining) collected during ERCP can be examined for the presence of viruses, protozoa, or neoplastic cells. [2],[3],[4]

Review of literature

REVIEW OF LITERATURE

The advent of highly active antiretroviral therapy (HAART) has dramatically reduced the clinical impact of infection with HIV1,2.The terminology "highly active antiretroviral therapy"(**HAART**) refers to use of combinations of three antiretroviral agents for treatment of HIV infection. To date, most clinical experience with use of HAART in treatment-naïve individuals has been based on three types of combination regimens: NNRTI based (1 NNRTI + 2 NRTI), PI-based (1-2 PI + 2 NRTI), and triple NRTI-based regimens. Most experience in India is with NNRTI based regimens.

HAART INDUCED LIVER DISEASE:

Highly active antiretroviral therapy (HAART) has dramatically changed the course of HIV infection, having decreased the morbidity and mortality derived from classical opportunistic infections. In the recent era of ART therapy (between 2000 and 2005), the estimated expected survival for a 25-year-old HIV-infected person was 39 years, compared with only 7 years for the same individual in the pre-ART era.[18]

Antiretroviral drug-related liver injury **(ARLI)** is a common cause of morbidity, mortality and treatment discontinuation in HIV-infected patients.[19] Prevention and management of ARLI have emerged as major issues among HIV-infected patients in the era of HAART.[20]Virtually every licensed antiretroviral medication has been associated with liver enzyme elevations, although certain drugs may cause liver injury more frequently

than others. Discerning the role of HAART in hepatotoxic reactions of HIV patients may be difficult due to frequent preexisting liver pathology, such as that arising from infection with hepatitis B or C virus. Moreover, poly pharmacy is common in HIV-infected individuals, and a very large number of medications are known to have effects on liver function and drug metabolism.

In addition, certain comorbidities, such as chronic hepatitis B (HBV) or hepatitis C (HCV) infection, may predispose patients to ARLI.[21] Several major mechanisms of ARLI have been described, including metabolic host-mediated injury, hypersensitivity reactions, mitochondrial toxicity, and immune reconstitution phenomenon. The management of ARLI should be based on its clinical severity and underlying pathogenic mechanism. Therefore, it is imperative to rule out other potential aetiologies before discontinuing HAART drugs.

CLINICAL IMPACT:

With the widespread use of HAART and the availability of new antiretroviral medications, ARLI has gained prominent attention owing to its negative impact on clinical outcomes. Drug-associated hepatotoxicity also creates an economic burden on already strained medical budgets, since additional visits and hospital admissions are often required for appropriate patient care and management.[19] Furthermore, antiretroviral drug discontinuation hampers maintenance of HIV suppression.

The severity of ARLI may range from the absence of symptoms to liver decompensation, and the outcome can range from spontaneous resolution to liver failure and death.[22],[23] In one study, severe hepatotoxicity with acute hepatic necrosis was recognized in 2% of HIV-infected patients dying from liver disease. Furthermore, in a large ACTG cohort of nearly 3000 patients initiating HAART, the most common grade 4 adverse events were liver related; this risk was increased in patients with underlying chronic viral hepatitis.[24]

Fortunately, the vast majority of episodes of ARLI are asymptomatic, and most ALT elevations resolve spontaneously, as described for many other medications, probably through a process called 'adaptation'.[25] However, in a minority drug-induced liver injury can be overt and have serious consequences. Therefore, it is critically important for the clinician to understand risk factors associated with poor outcomes and the pathogenic mechanisms of disease.

In a recent American study, which evaluated the causes of death of HIV-infected individuals, discontinuation of ART due to hepatotoxicity increased from 6% in 1996 to 31.8% in 1998-1999 among those mortalities . More recently, Kramer and colleagues have highlighted the increase in the number of cases of fulminant liver failure in HIV/HCV-coinfected individuals during the HAART era, even after excluding patients with advanced liver disease and adjusting by alcohol intake.

Drug liver toxicity has impacted on the recommendations for antiretroviral therapy in certain scenarios. Thus, the use of nevirapine (NVP) has been recommended to be avoided as part of post-exposure prophylaxis regimens. The reason for that was the occurrence of fulminant hepatitis in two cases and severe liver toxicity in 12 other healthy subjects who received a NVP-including HAART regimen after HIV exposure.

However, NVP seems to be safe when administered to mother and child as a single dose for prevention of mother-to-child HIV transmission.[3],[4]

DEFINITION OF LIVER INJURY:

ARLI is defined by elevations in liver enzymes in serum, with alanine aminotransferase (ALT) characteristically greater than aspartate aminotransferase (AST). To date, there has been broad variability in the criteria used in clinical studies to categorize the severity of hepatotoxicity. Some studies have utilized ALT parameters as minimal as two times the upper limits of normal.[26]while others have employed an absolute threshold (e.g., >100 IU/ml), regardless of baseline liver function tests.[27] The clinical relevance of these elevations is uncertain.

More recently, the AIDS Clinical Trials Group (ACTG) has defined a grading scheme against the patient's baseline serum aminotransferase concentrations. For example, in patients with a normal prêtherapy ALT or AST, hepatic injury is graded as moderate or severe based on a 5-fold or 10-

fold increase in aminotransferases, respectively.[28]In patients with abnormal liver enzymes prior to therapy, a >3.5-fold or a 5-fold increase in ALT or AST is considered indicative of moderate or severe hepatotoxicity, respectively.[29]

DEFINITIONS OF HAART-ASSOCIATED HEPATOTOXICITY:

The AIDS Clinical Trials Group currently uses the following toxicity grading scale:

PATIENTS WITH NORMAL PRETREATMENT ALT/AST:	
Grade 0 hepatotoxicity	**<1.25 times the ULN (upper limit of normal)**
Grade 1 hepatotoxicity	**1.25 to 2.5 times the ULN**
Grade 2 hepatotoxicity	**2.5 to 5 times the ULN**
Grade 3 hepatotoxicity	**5.1 to 10 times the ULN**
Grade 4 hepatotoxicity	**>10 times the ULN**

There is a grading scale for the HAART-associated cholestasis:	
Grade 0 cholestasis	**<1.1 times the ULN**
Grade 1 cholestasis	**1.1 to 1.5 times the ULN**
Grade 2 cholestasis	**1.6 to 2.9 times the ULN**
Grade 3 cholestasis	**3 to 5 times the ULN**
Grade 4 cholestasis	**>5 times the ULN**

For patients with elevated pre-treatment ALT/AST, changes are compared to baseline rather than upper limit of nomal. Grades 0 and 1 are identical, but grade 2 is associated with ALT/AST 2.6 to 3.5 times baseline,

grade 3 is 3.6 to 5 times baseline, and grade 4 greater than 5 times baseline.[30] Severe hepatotoxocity is defined as grade 3 or 4 change in transaminase levels.

Liver function test abnormalities require careful interpretation. On the one hand, some drugs (e.g., nevirapine and less frequently efavirenz) increase γ-glutamyl transpeptidase serum levels. This laboratory result is often misinterpreted as a marker of liver damage, when isolated elevation of this enzyme actually reflects enzyme induction. Similarly, hyper bilirubinaemia alone should not be equated with liver injury, since indirect hyper bilirubinaemia may be related to medications, such as indinavir or atazanavir.[31],[32],[33] This risk is increased in patients with underlying Gilbert's syndrome, a genetic disorder .

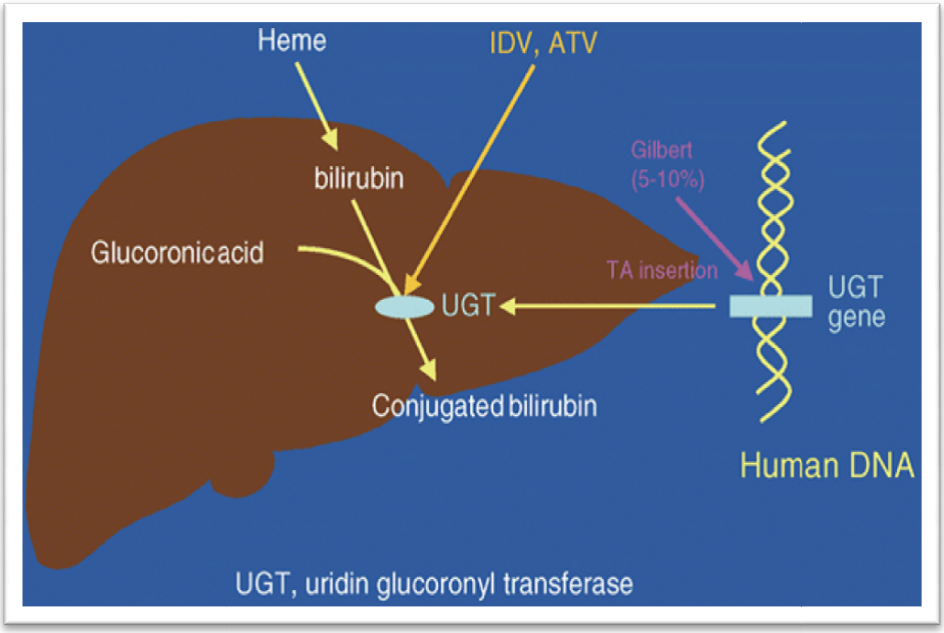


Figure 2.1-Interplay between bilirubin metabolism, Gilbert's genotype and atazanavir (ATV) or indinavir (IDV) use.

On the other hand, drug-induced liver injury that is associated with an elevated direct bilirubin and clinical jaundice portends a poor clinical outcome. A cholestatic profile should only be considered when there is an associated increase in serum alkaline phosphatase as well as bilirubin. Elevated aminotransferases also need to be interpreted within their clinical context. For example, increased liver enzymes in a patient with chronic HBV infection do not necessarily imply drug injury but may reflect HBV-related hepatic flares, which often occur during the natural course of the disease.

INCIDENCE AND RISK FACTORS:

After initiating HAART, the reported incidence of severe liver toxicity ranges from 2 to 18 %.[21],[27],[29],[34-42]Differences in study outcomes may reflect heterogeneity in patient populations, frequency of liver enzymes determinations, other exogenous exposures (e.g., alcohol), medication prescribing patterns, prevalence of chronic viral hepatitis, and criteria used for defining severe hepatotoxicity.

Hepatitis B and C co-infections:

Liver toxicity, especially severe toxicity (grades 3 and 4),is clearly more frequent in HCV and/or HBV co-infected individuals treated with HAART.[33],[22-25],[34-38]In one study, a higher risk of hepatotoxicity was found in patients carrying HCV genotype 3 (HCV-3) compared to other genotypes.[40] The clinical implications of this finding are 2-fold. On one hand, the presence of HCV-3 may impact on the selection of HAART

regimen, choosing those with less potential for hepatotoxicity. On the other hand, since genotype 3 shows a higher response to α-interferon (IFN)and ribavirin (RBV), anti-HCV treatment should be given if no major contraindication is present.

In addition to drug injury, flares in serum transaminase concentrations in a patient with chronic HBV can be related to several different factors, including viral rebound after withdrawal of effective anti-HBV therapy, break through of drug-resistant HBV strains or spontaneous flares of HBV viraemia.[41],[43-45]The clinician must bear this in mind before misinterpreting hepatic flares as drug injury.

Alcohol:

Alcohol is a known heaptotoxin and its use has been associated with an increased risk of ARLI in the studies that have examined this variable.[21]Chronic use may also predispose to hepatocyte injury by increasing oxidative damage to mitochondrial DNA and depleting stores of glutathione, an important scavenger of free oxygen radicals.[46]

Other Predisposing Factors:

Multiple studies have demonstrated that the risk of liver injury is increased in those with aminotransferase elevations prior to initiating HAART.[35],[37-40] Other risk factors associated with ARLI include older age [7],female gender[40],[47],first exposure to antiretroviral treatment[41] and significant CD4 cell gains following HAART initiation.[29,48] More recently,

an association between the presence of advanced stages of liver fibrosis and greater risk of ARLI has been reported.[49]The mechanism for this observation is unclear, but it could be the consequence of compromised hepatic clearance with subsequent drug overexposure in patients with cirrhosis.[84]

ANTIRETROVIRALS:

Studies that have evaluated the risk of liver injury associated with a particular antiretroviral agent or class are often conflicting. The effect of a specific drug is difficult to ascertain because of the widespread use of combination therapy.

Nucleoside Reverse Transcriptase Inhibitors:

NRTIs are associated with low incidence of elevated liver enzyme values, **5% to 6%**[29],[51],[52] ranging from 7% with zidovudine, 9-13% with stavudine and 16% with didanosine.[53]Newer NRTI such as emtricitabine, abacavir and tenofovir are associated with a low incidence of mild asymptomatic aminotransferase elevations.[54]

Mitochondrial toxicity is an infrequent but distinctive type of hepatotoxicity associated with the use of NRTI that may evolve to acute liver failure with severe hepatomegaly and lactic acidosis.[55]This complication generally occurs after several weeks or months of NRTI treatment. However, nucleoside analogues differ widely in their propensity to induce mitochondrial toxicity. Potency estimations in vitro gave a

descending hierarchy of their potency: zalcitabine, didanosine, stavudine, zidovudine and, finally, abacavir, as least toxic.[54]In-vitro data support additive or synergistic mitochondrial toxicity of some NRTI combinations [56]such as stavudine and didanosine.[56-58]

Two clinical entities of hyperlactatemia are associated with mitochondrial toxicity. The time to presentation of NRTI-related hyperlactatemia is reported to be 3 to 20 months, with a median time of 9 months. Many patients have a 2- to 4-week prodrome, the most common symptoms are nausea, vomiting, vague abdominal pain, and abdominal distension, the prognosis is usually good as long, as the use of NRTIs is stopped, but long-term sequelae may occur. The second associated mitochondrial injury is the lactic acidosis syndrome, reported to occur 1 to 4 Cases/1000 patient-years. This condition is much more ominous and is associated with multiorgan failure and a mortality rate of 30% to 100% even if ART is stopped.[59]

Hypersensitivity reactions have been linked to abacavir and are characteristically seen in patients with HLA-B*5701 background.[60]Re exposure to abacavir can be fatal.Incidents of unexplained liver disease in HIV-infected individuals have recently been reported in which clinical manifestations of portal hypertension are often predominant. Didanosine exposure seems to be involved in almost all and nodular regenerative hyperplasia is a frequent histological finding.[61,62]

Nonnucleoside Reverse Transcriptase Inhibitors:

The incidence of elevated liver enzyme values with either drug has been reported to range from less than **2% to 20%.**[63],[64] However, severe liver toxicity, occurring with early latency, has been reported in HIV-infected and HIV-seronegative individuals. Warnings against the use of nevirapine for post exposure prophylaxis were issued after some individuals developed hepatic failure requiring liver transplantation.[65]Concomitant use of NNRTIs and PIs also seems to increase the risk of elevated liver enzyme values.[66],[67],[68]Women who have CD4 counts higher than 250 cells/mL are especially at risk for nevirapine-related fulminant hepatic failure.[69]Several studies continue to find women at greater risk than men for elevated liver enzyme values, especially with nevirapine, this finding remains unexplained.[70],[71]

Nevirapine seems to be associated with two types of toxicities. An initial hypersensitivity reaction characterized by rash, fever, and elevated liver enzyme values occurring in the first 4 to 6 weeks is thought to represent an idiosyncratic reaction of the host and is not related to the dose of the drug. For reasons that are unclear, women who have CD4 counts of 250 Cells/ml and higher and men who have CD4 counts of 400 cells/ml or higher Seem to be at increased risk of this type of toxicity.[72] Furthermore, a low body mass index is another independent risk factor for nevirapine hypersensitivity reaction.[70]

In addition, nevirapine has been associated with a late risk of toxicity occurring at 6 to 12 months.[73-75]This type of toxicity seems to increase in incidence over time, probably results from a direct effect of the drug, and is thought not to represent an immune- mediated process. Persons with an HLA-DRB1*0101 background have an increased propensity for developing nevirapine-associated hypersensitivity.[76-78]

Idiosyncratic Drug-related Toxicity:

In other studies, a different pattern of drug injury with nevirapine use has emerged, with onset of liver enzyme elevations occurring beyond 16 weeks of therapy, consistent with direct or idiosyncratic host-mediated liver injury.[47],[48]This late onset of hepatotoxicity with NNRTI is more common in patients with underlying chronic viral HBV and/or HBV&HCV infection, as has been described with many other antiretroviral agents. In patient populations that vary in terms of chronic viral hepatitis prevalence, NNRTI-associated liver injury can vary from 15%[48] to as low as 3%.[79]Specific genetic polymorphisms of metabolizing enzymes and drug transporters may also increase the risk of this complication.[80,81] It should be highlighted that hepatotoxicity with either nevirapine or efavirenz does not appear to increase the risk of developing liver injury on exposure to the alternative NNRTI.[82],[83]

Protease Inhibitors:

The phenomenon of ARLI became more evident after the introduction of PI drugs. Rates of hepatotoxicity from registration trials of various PI have ranged from **1% to 9.5%,** but few patients had serious liver-related outcomes.[85]In comparison with other drugs in its class, full-dose ritonavir has consistently been shown to be more hepatotoxic.[29],[37],[41]However, the use of low-dose ritonavir for pharmacokinetic boosting of other PI drugs appears to be safe.[86]

Although there are a few case reports of liver-related toxicity with indinavir, these were in association with advanced liver disease; dose reduction is recommended in patients with cirrhosis. Several cases of clinical hepatitis and hepatic decompensation, including some fatalities, have been associated with the use of tipranavir, particularly in patients with chronic HCV infection.[87],[88] Nelfinavir, saquinavir, atazanavir, fosamprenavir, lopinavir and darunavir are associated with a relatively safer liver toxicity profile.[89-96] Amprenavir has occasionally been associated with drug-related hypersensitivity reactions but only sporadically with severe hepatotoxicity.[97]

In patients taking PIs, the incidence of elevated liver enzyme values is higher in those who have HIV/HCV coinfection than in those who have HIV alone. Recently, an FDA black-box warning was issued for the use of ritonavir to boost tipranavir because of increased hepatotoxicity in

coinfected patients. Multivariate analysis also has shown that an increase in CD4 counts to more than 50 cells/mL from baseline, which may indicate an underlying immune- mediated process, is associated with increased risk of elevated liver enzyme values.[98]

New Antiretroviral Drug Families

The clinical development of aplaviroc, a CCR5 antagonist, was halted in 2005 after the occurrence of severe hepatotoxicity.[99]In contrast, maraviroc and vicriviroc appear to have safer hepatotoxicity profiles. Enfuvirtide, the only approved fusion inhibitor, has demonstrated a consistent safety record in terms of liver toxicity.[100]Data on integrase inhibitors are still scarce, but to date MK-0518 has not been associated with any significant liver toxicity.[101]

Table 2.1 - Liver toxicity of commonly used anti- HIV medications

Drug type	Drug name	Pattern of injury	Comments
Protease inhibitor	Indinavir Saquinavir Nelfinavir Ritonavir	Hepatocellular, distinct histologic pattern including hepatocyte ballooning, Kupffer cell activation, pericellular zone 3 fibrosis	< 10% of patients have transaminases > 5 ULN Ritonavir inhibits P 450
NRTI	ddC d4T ddl AZT	Microvesicular steatosis	Mitochondrial toxicity manifesting as lactic acidosis
NNRTI	Nevirapine Efavirenz	Hepatocellular	NVP associated with grade 4 toxicity; FDA alert

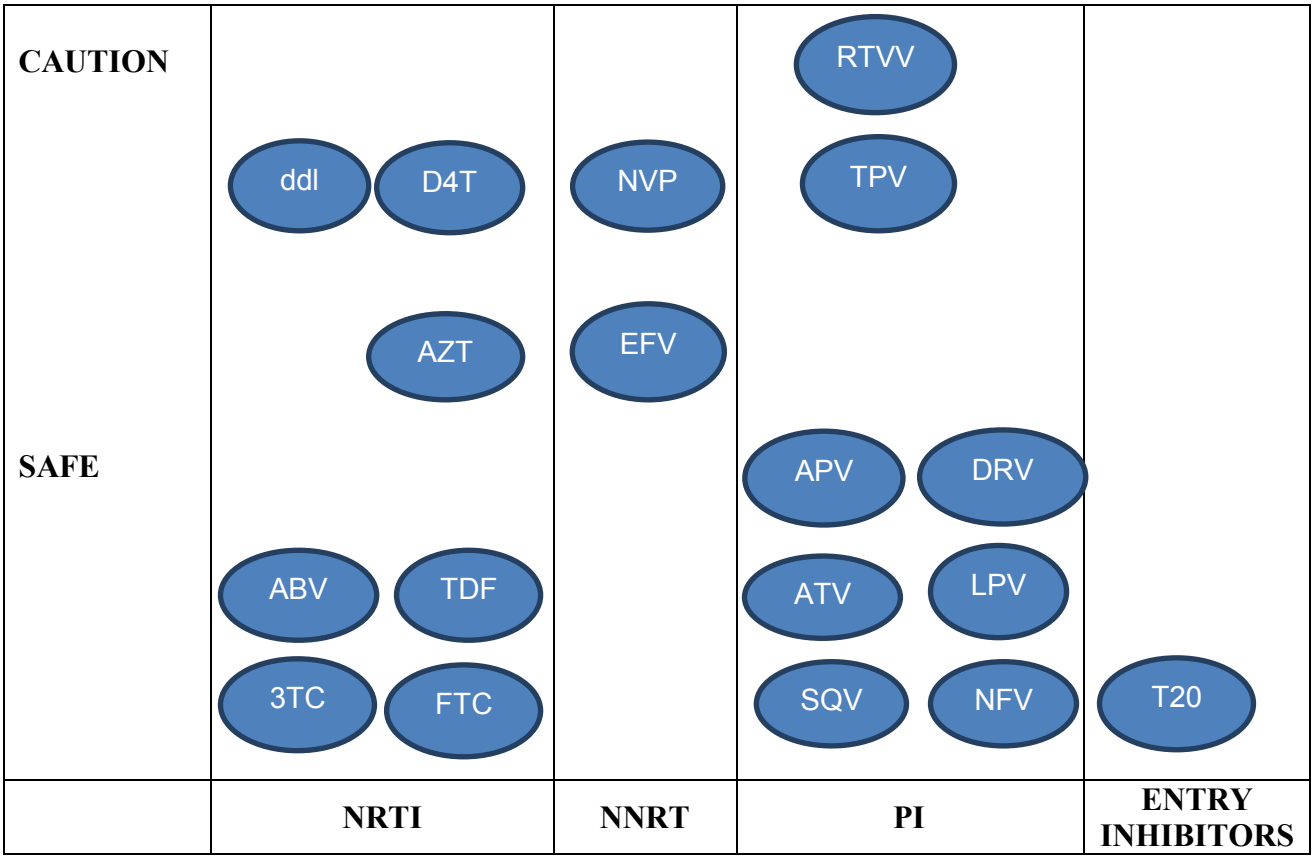


Figure 2.2 - Hepatic safety profile of antiretroviral drugs

Table 2.2 - Common causes and risk factors

COMMON CAUSES AND RISK FACTORS
Drugs
Obesity
Coinfection with hepatitis viruses
Advanced disease
Older age
Female gender
First exposure to antiretroviral treatment
Significant CD4 cell gains following HAART initiation.

MECHANISMS OF LIVER TOXICITY:

Drug-induced liver injury can be considered predictable (high incidence) or unpredictable (low incidence).[102]Liver injury may result from direct toxicity of the drug or its metabolites or may be an idiosyncratic response in persons with a characteristic genetic predisposition. The latency period between the initiation of therapy and the onset of liver disease provides clues to its aetiology.

Predictable hepatotoxic reactions are dose dependent and host independent, with the classic example being paracetamol (acetaminophen) toxicity. Early-onset toxicity (within a few days) is strong evidence for direct drug toxicity, particularly if there has been no previous exposure. Unpredictable hepatotoxic reactions are host dependent and not dose related.[103]Unfortunately, the vast majority of drug reactions are

unpredictable. They occur when the drug is transformed into an intermediate metabolite that is either toxic (host-mediated metabolism) or provokes an immunological response (hypersensitivity reaction).

Table 2.3 - Clinical presentation of Hepatotoxicity

	EARLY ONSET	**LATE PRESENTATION**
Interval	1-8 weeks	2-12 months
Mechanism	Immune Mediated	Host-mediated idiosyncratic
Role of Hepatitis C Virus	No	Yes
Role of CD4 counts	Yes	No
Drugs(E.g)	Nevirapine, Abacavir	Stavudine, Didanosine Ritonavir

Table 2.4- Mechanisms of Hepatotoxicity

MECHANISMS OF HEPATOTOXICITY
Direct toxicity
Hypersensitivity reaction
Mitochondrial toxicity
Metabolic abnormalities
Immune reconstitution syndrome in HBV/HCV co-infection

Metabolic Host-mediated Injury:

Host differences in drug metabolism may lead to an excess of potentially harmful reactive drug metabolites when genetic polymorphisms affect critical metabolizing enzymes.[104]The latency of onset is long (from 2

to 12 months), which poses problems for patient monitoring.[105].Prototypical examples include isoniazid and troglitazone, these aberrant metabolic pathways may also underlie one form of drug injury seen in association with the nonnucleoside reverse transcriptase inhibitors (NNRTI) and the protease inhibitors (PI).[106],[107]

Some drugs may potentiate the activation of T cell death receptors and/or intracellular stress pathways, leading to increased oxidative stress.[108]In response, hepatocytes promote mechanisms of cytoprotection, such as the formation of heat shock proteins, which protect the liver against toxic metabolites.[104] This cytoprotective response may explain the spontaneous normalization of liver enzymes that may occur despite maintenance of HAART (or other medications, such as isoniazid). Alternatively, the rise and fall of serum aminotransferase concentrations after initiation of medications may be related to a phenomenon of 'adaptation', whereby liver function tests normalize despite ongoing drug exposure.[109]

Hypersensitivity Reactions:

Allergic phenomena are idiosyncratic to the host, have an intermediate onset of latency (from a few days to 8 weeks) and are not dose related. The incidence of hypersensitivity reactions is about 1 in 1000 in the general population but is more common in patients with HIV.[110] Prototypical examples include phenytoin and sulphonamides, which can cause rash,

fever, eosinophilia and hepatitis. The temporal relationship between symptoms and signs and the initiation of the suspected culprit drug are helpful in distinguishing this type of drug reaction. Clearly, rechallenges should be avoided if drug hypersensitivity is suspected.

Hypersensitivity reactions have been reported with nevirapine, abacavir and less frequently with amprenavir, both in HIV-infected patients and in subjects receiving HIV prophylaxis after potential exposure.[111] These immune-mediated drug reactions may involve the generation of neoantigens formed by the covalent bonding of liver proteins with reactive drug metabolites.[104],[112]

Mitochondrial Toxicity:

Mitochondria play a major role in energy production and glucose and fat metabolism, but they are also the main source of reactive oxygen species, which can lead to cellular demise. The most infamous example of severe mitochondrial damage occurred with the use of the nucleoside analogue fialuridine for the treatment of HBV. During the initial stages of the study, several participants developed lactic acidosis and hepatic failure.[113] Chronic therapy with nucleoside reverse transcriptase inhibitors (NRTI) for the treatment of HIV can also lead to mitochondrial toxicity after long-term exposure. This drug class selectively inhibits DNA polymerase-γ, which is responsible for replication of mitochondrial DNA. Diminished mitochondrial function may lead to a decrease in oxidative phosphorylation,

which in turn leads to aberrations in pyruvate metabolism and accumulation of lactate.[114]

The presence of chronic HCV infection, which is quite prevalent in HIV-infected patients may increase a patient's susceptibility to antiretroviral drug-related mitochondrial stress and damage.[115]HCV core protein causes mitochondrial injury, leading to excessive production of reactive oxygen species.[116-118] This leads to oxidative stress, which is enhanced in the presence of tumour necrosis factor, alcohol or nucleoside analogues. Consequently, exposure to any nucleoside analogues either for the treatment of HIV (e.g., didanosine) or for HCV [e.g., tribavirin (ribavirin)] may further enhance mitochondrial toxicity.[119]

Immune Reconstitution Phenomena:

ARLI associated with HAART-induced CD4 T cell recovery has been attributed to immune reconstitution phenomena, particularly in the setting of chronic HBV and occasionally in patients with chronic HCV.

Hepatitis B. Cell-mediated immunity plays a central role in the pathogenesis of chronic HBV.[120] For example, in an HIV/HBV coinfected patient with advanced immunosuppression, HBV replication generally increases but HBV-related liver inflammation lessens and transaminase levels decline.[121] Conversely, when HAART is initiated improved cellular immunity can lead to flares in liver enzymes [122] and spontaneous seroconversion [123] even in the absence of any anti-HBV active

drug.[124]Liver enzyme flares in HIV/HBV-coinfected patients taking antiretroviral therapy need to be carefully interpreted with concomitant evaluation of serum HBV DNA in order to assign causality correctly. Liver enzyme elevations in HIV/HBV-coinfected patients following initiation of antiretroviral therapy can be caused by (i) direct drug-related liver injury (ii) immune reconstitution in patients positive for HBV surface antigen (HBsAg), (iii) seroconversion in patients positive for HBV 'e' antigen and/or HBsAg, (iv) HBV reactivation in inactive carriers and occasionally in those with resolved HBV infection.

Hepatitis C. However, antibody responses to HCV do not necessarily correlate with reconstitution of cellular immune function and initiation of HAART does not imply restoration of HCV-specific T cell responses.[125] Moreover, the role that cellular immunity plays in the pathogenesis of chronic HCV is not as clear as for HBV.[120]Finally, conflicting results have been reported on whether gains in absolute numbers of CD4 T cells correlate with flares of transaminases.[135],[136],[126],[127]Although immune reconstitution remains an attractive theory and it may certainly explain clinical events in a subset of HIV patients with HCV [128],[129] more evidence needs to be gathered before any conclusions can be drawn.

Novel Potential Mechanisms for Antiretroviral Drug-related Injury: Hepatic Steatosis:

Insulin resistance, hyperlipidaemia and visceral adiposity are the metabolic and morphological abnormalities that have been intrinsically linked to the development of hepatic steatosis in the general population. [130] These same metabolic and morphological aberrations coexist in a high percentage of HIV-infected patients and are known as the **lipodystrophy syndrome.**[131] Several studies have found that hepatic steatosis is highly prevalent in HIV-seropositive patients, particularly in those with chronic HCV and/or receiving NRTI drugs with high mitochondrial toxicity profiles.[132],[133]

Hepatic steatosis produces substrates for lipid peroxidation; this results in the basal formation of potentially harmful reactive oxygen species, which can lead to liver injury.[134],[136] Furthermore, HCV genotype 3 infection, which induces hepatic steatosis through a virally mediated cytopathic effect has been associated with an increased risk of ARLI.[137-139]These studies suggest that liver steatosis itself may be a predisposing factor for drug-related toxicity

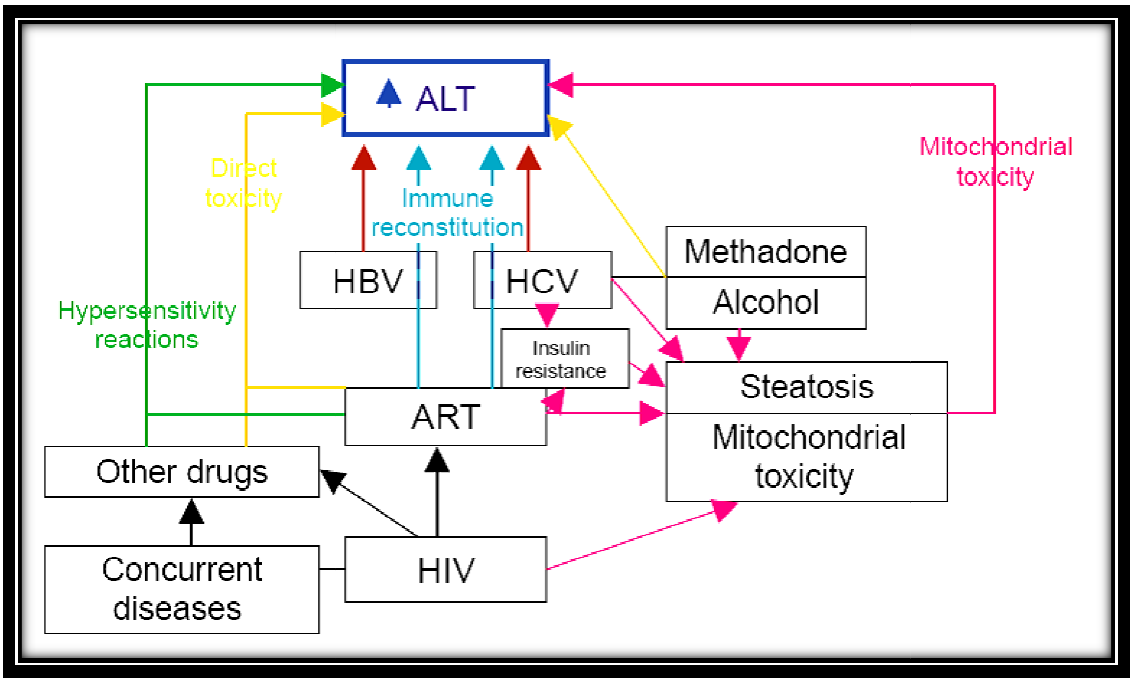


Figure 2.3 -Mechanisms of Hepatotoxicity

THERAPEUTIC MANAGEMENT:

When Should Antiretroviral Drugs Be Discontinued?

Clinical decision making regarding drug discontinuation is often a balancing act. Stopping medications at the very first sign of mild injury can prevent serious consequences. However, this approach can sacrifice potentially important therapy for a large number of patients. Continuing with therapy, however, can lead to untoward outcomes. For patient safety, several important principles need to be emphasized.

- Symptomatic hepatitis is of much greater concern than asymptomatic elevations of transaminases. The longer a patient continues to take a drug after onset of symptomatic hepatitis, the more likely the outcome will lead to serious liver injury.

- ARLI associated with overt jaundice with increased direct bilirubin levels has a high mortality rate. Medications should be immediately discontinued.
- If a patient complains of symptoms consistent with mitochondrial toxicity in association with an elevated lactate level, medications should be immediately discontinued.
- If the patient has symptoms consistent with drug hypersensitivity, the medication should be stopped immediately and readministration can be fatal.
- Medications should be discontinued promptly if plasma ALT or AST is greater than 10 times the upper limit of normal (grade 4), even if the patient is asymptomatic.[140],141]For patients with advanced liver disease, more conservative management should be exercised to avoid hepatic decompensation

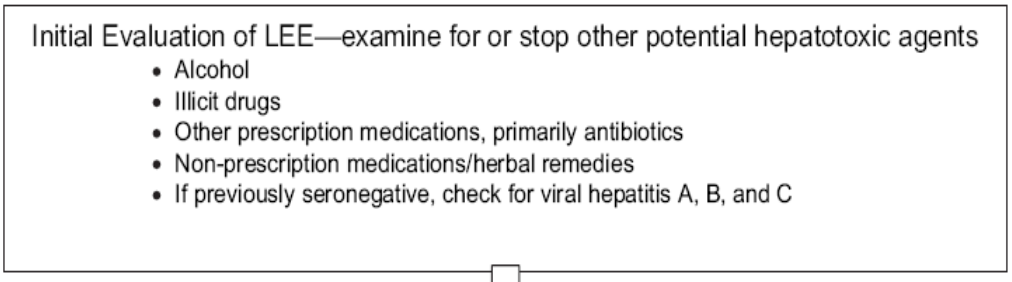
Spontaneous Improvement in Transaminases Despite Drug Continuation:

In assessing drug toxicity, mild elevations of serum transaminases are commonly seen and often improve despite administration of the same drug.[142] This has also been observed with the antiretroviral medications, particularly with PI use. Based upon these data, some authors have suggested that PI-containing HAART does not need immediate adjustment but simply careful monitoring.[143] It should be emphasized that most of these patients had asymptomatic elevations of transaminases.

Always consider alternative causes for hepatitis including viral hepatitis, cholecystitis, opportunistic infections and alcohol or cocaine use.

Table 2.5- Monitor for Liver Enzymes and Hepatotoxicity Symptoms

Time After Initiation of HAART	**Monitor for Liver Enzymes and Hepatotoxicity Symptoms**
0–1 month	Every 2 weeks
18 weeks	Monthly
Week 19 onward	Every 3 months



Class of Injury	Signs and Symptoms	Associated Drugs	Action(s)
Hypersensitivity reaction	Fever, rash,	• nevirapine • abacavir • efavirenz	Stop offending drug and modify ART regimen
Mitochondrial toxicity/lactic acidosis	Weight loss, N/V, abdominal pain	• zidovudine • didanosine • stavudine	Stop ART, can give modified ART once signs and symptoms resolve
Hepatitis B flare	Asymptomatic; RUQ pain, N/V	• lamivudine • emtricitabine • tenofovir	Measure HBV DNA; continue active HBV agent(s) as part ART
Hepatitis C flare	May be asymptomatic	• any ART	HCV treatment may be needed to allow ART to be tolerated
Other Hepatocellular injury	Asymptomatic	• ritonavir • nevirapine • efavirenz	Stop ART, assess most likely agent and modify ART
Cholestatic Injury	Jaundice	• No specific drug; • Caused by any severe hepatocelluar injury	Stop ART

N/V= nausea and vomiting; RUQ= right upper quadrant pain; HBV= hepatitis B;

Figure 2.4 - Algorithm for the management of patients with ART-related Hepatotoxicity.

Aim of the study

AIM OF THE STUDY

The study was conducted with the objective of

1. Estimation of incidence of drug induced hepatotoxicity in patient receiving HAART therapy for HIV/AIDS
2. To analyse the risk factors that are associated with drug induced hepatotoxicity in these patients.

Materials & methods

MATERIALS & METHODS

About 1250 patients who receive ART were screened and patients with evidence of liver dysfunction were isolated. Study population was selected as follows.50 adult patients of both sexes infected with HIV and fulfil the WHO criteria for clinical AIDS receiving HAART for a period of more than 1 month were included in the study**.**

Table 4.1 – Patient Selection

PATIENT SELECTION
INCLUSIVE CRITERIA Patients with HIV infection i. who receive HAART therapy for > 1 month
EXCLUSION CRITERIA i. Patients with base line LFT abnormal ii. Evidence of extrahepatic cause of jaundice iii. Past history of jaundice iv. Clinical evidence of liver disease at the institution of HAART v. Antenatal mothers vi. Children < 13 years

PROTOCOL

1. All patients who receive HAART therapy who met the above criteria were included in the study
2. The following were noted in each patient

    i. Age

    ii. Sex

    iii. BMI

    iv.Alcohol usage

    v. Smoking

    vi. H/o jaundice in the past

    vii. Drug allergy

    viii.Diabetes

    ix. Tuberculosis (pulmonary/ extra pulmonary)

    x. Mode of acquisition of HIV

    xi. Nadir CD4 count

    xii. Latest CD4 count

    xiii. Socio economic status

    xiv. Dose of each drug

    xv. Duration of therapy of each drug

    xvi. Drug withdrawal

    xvii. Other adverse reaction with the drug

    xviii. Antitubercular therapy (ATT)

xix. Antifungals

xx. Antibiotics

3. Base line LFTs were measured

4. Those who have abnormal LFT following were noted

a) USG
b) HBsAg, anti HCV antibodies
c) Chest X ray
d) Complete blood count
e) Bleeding time

THE STUDY

STUDY DESIGN	:	Retrospective Analytical Study
VENUE	:	Tirunelveli Medical College & Hospital, Tirunelveli
DURATION	:	12 months

COLLABORATING DEPARTMENTS

ART CLINIC, Tirunelveli Medical College & Hospital, Tirunelveli

LIVER CLINIC, Tirunelveli Medical College & Hospital, Tirunelveli

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STASTICAL ANALYSIS

Statistical analyses were made by One way ANOVA F test using **SSPS software.**

RISK FACTORS FOR HEPATOTOXICITY FOLLOWING HAART

IN HIV PATIENTS

PROFORMA

S.NO.

NAME AGE SEX UNIT

OCCUPATION: ADDRESS

CONTACT NO. HOSPITAL NO

SYMPTOMS

PRIMARY SYMPTOMS :

GI SYMPTOMS

Fever

Jaundice

Loss of appetite

Loss of weight

Pruritus

GI bleed

PAST HISTORY :

Jaundice

Abdominal surgery

Blood transfusions

Hepatotoxic drug intake

Alcohol /Smoking

Tobacco usage of other means

IV Drug Use

Drug abuse

Marital status

Promiscuity M2F / M2M

SIGNS :

General

Weight height

Nutrition

BMI

Pallor

Oral lesions

Jaundice

Evidence of liver cell failure

Ascites

Cutaneous bleed

Hepatic encephalopathy

DURATION OF HAART:

Table 4.2 – Duration of HAART

DRUGS	DOSE	Started on	Stopped on

ATT

Table 4.3 – ATT

DRUGS	DOSE	DURATION

OTHER ANTIVIRALS, ANTIFUNGAL

Antibiotics

Other drugs

Pretreatment LFT Serial LFT

HBsAg Anti HCV

Results

RESULTS

Baseline data

Total screened : 1250

Study population consists of 50 consecutive patients with evidence of liver dysfunction.

Incidence of Hepatotoxicity :4%

Mortality : 2 %

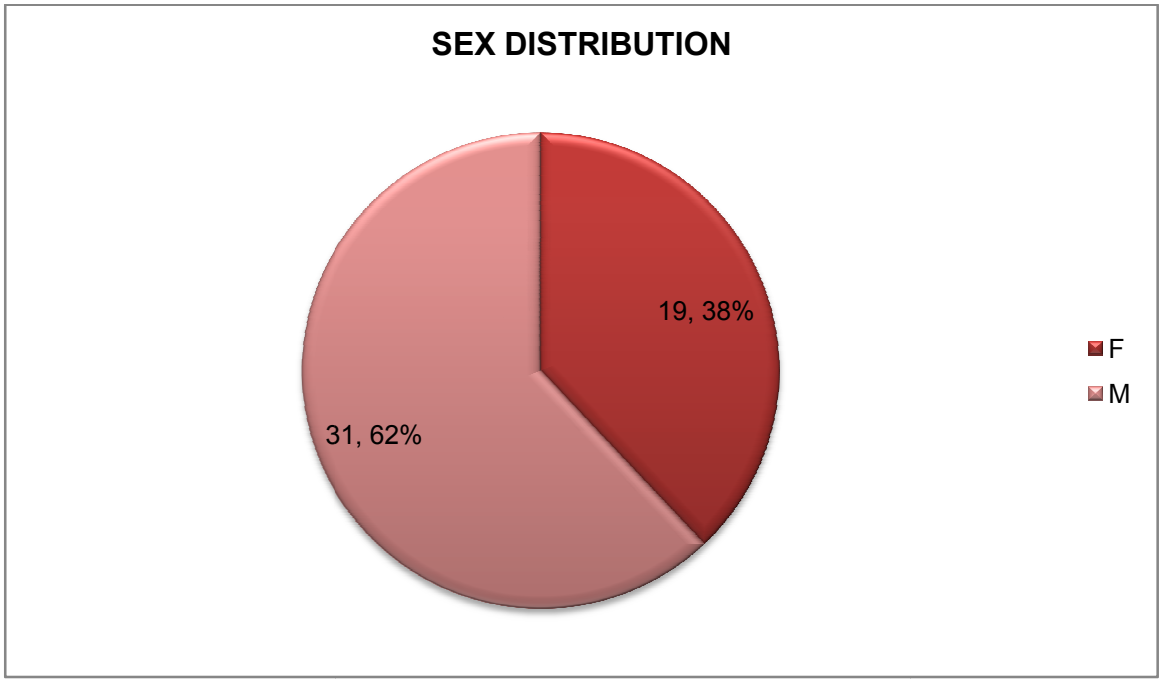

Figure 5.1 – Sex Distribution

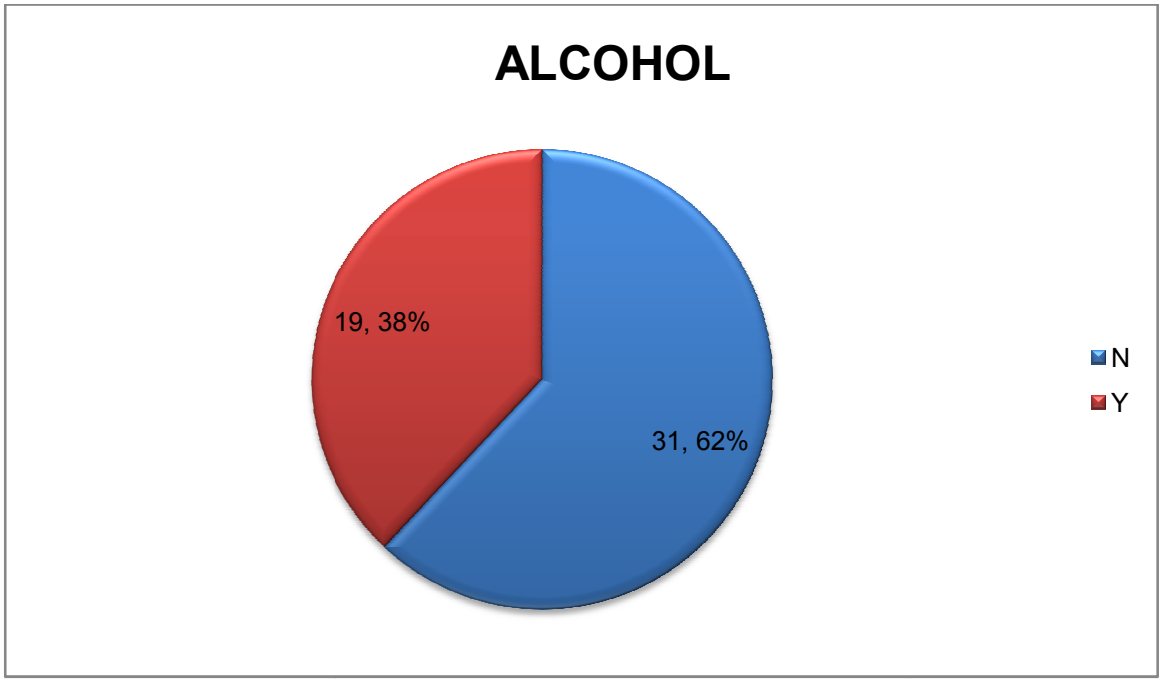

Figure 5.2 – Alcohol

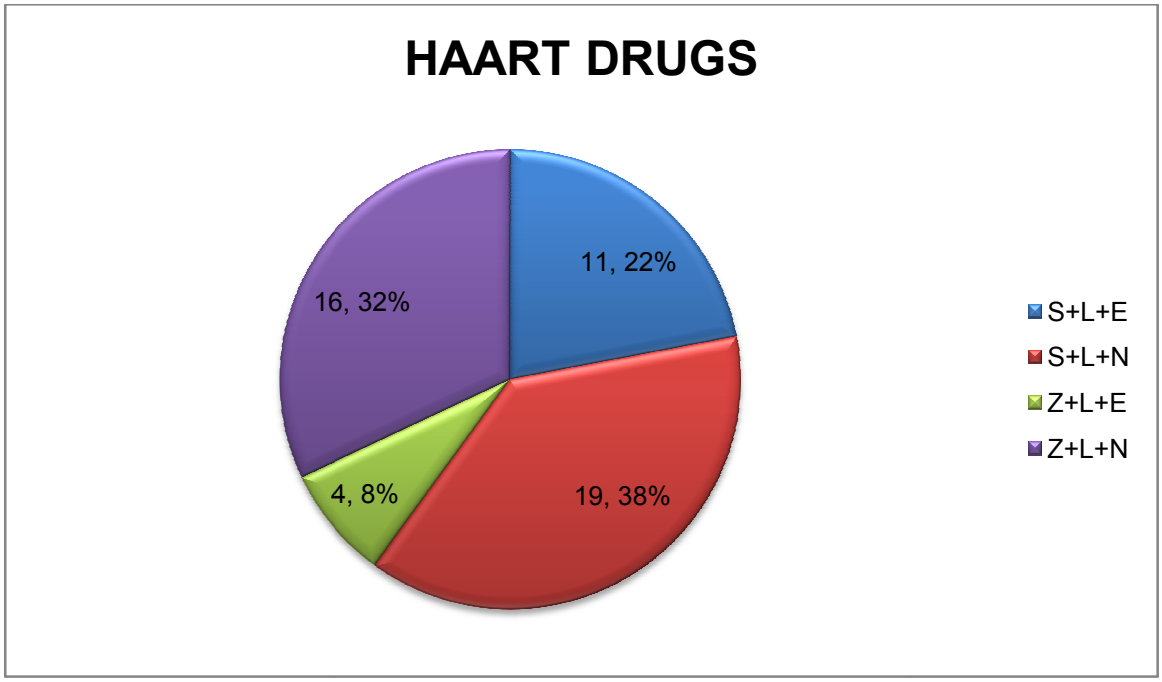

Figure 5.3 – HAART Drugs

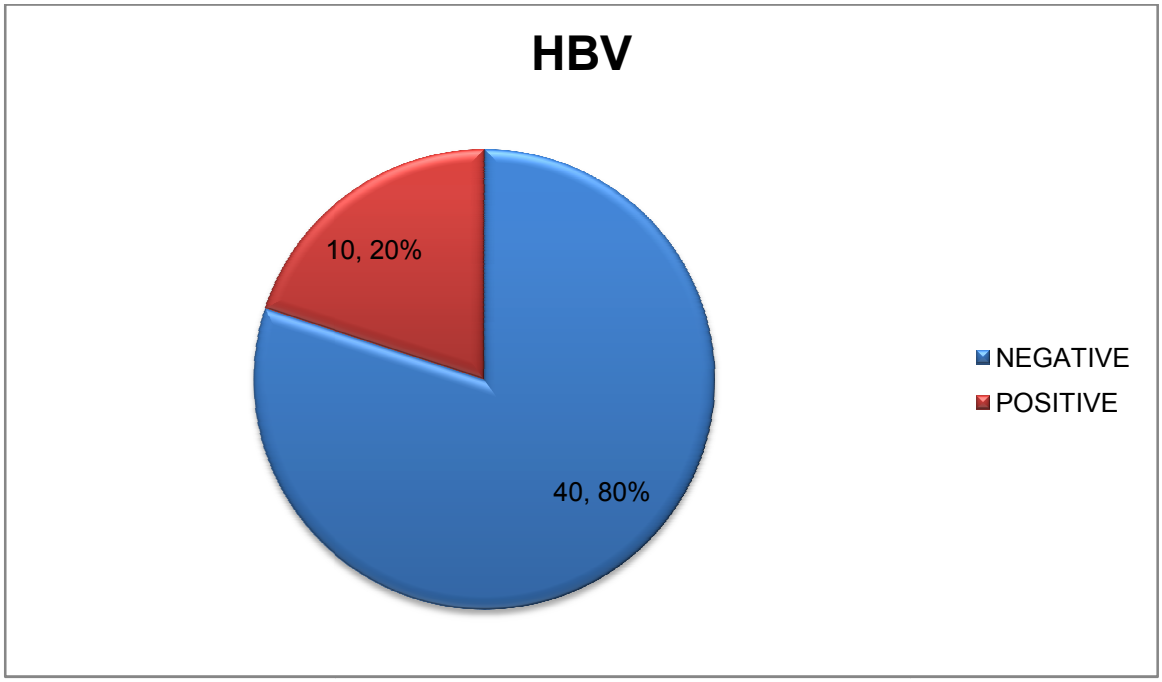

Figure 5.4 – Incidence of HBV

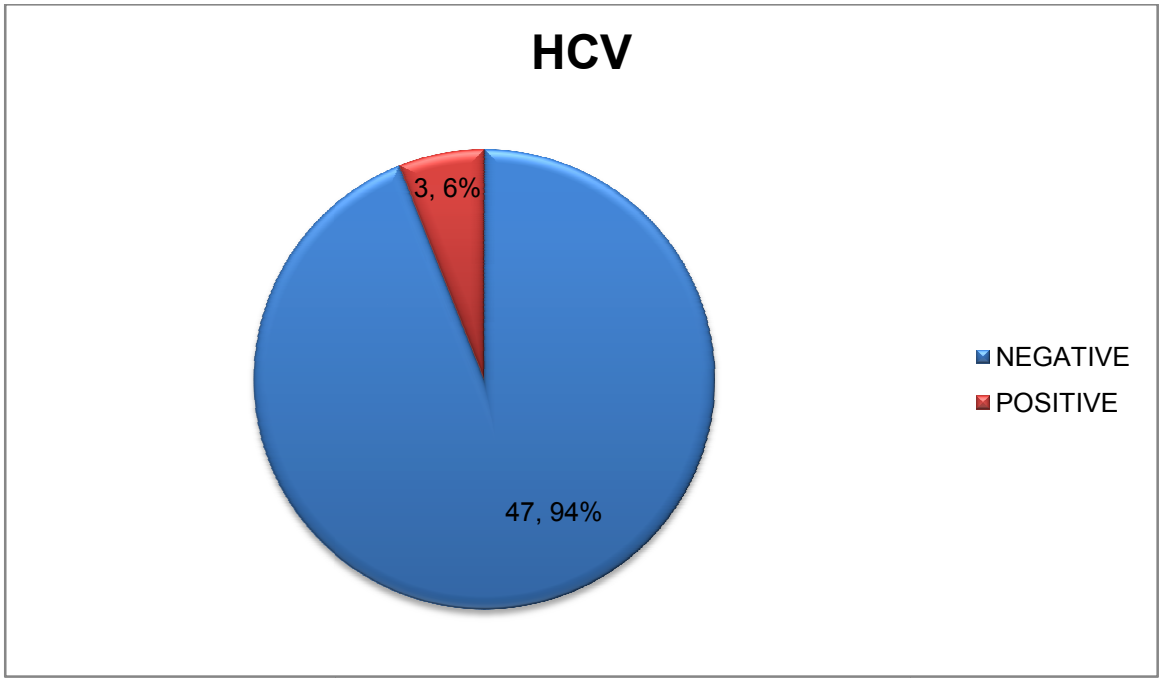

Figure 5.5 – Incidence of HCV

Descriptive Statistics

Table 5.1 – Descriptive Statistics

	N	Min.	Max	Mean	S.D
AGE	50	23	58	38.92	8.926
BMI	50	14.2	25.7	18.982	2.5976
CD4COUNT	50	41	184	105.42	31.031
TB	50	3	7	4.40	0.910
SGOT	50	250	397	332.10	45.651
SGPT	50	235	499	395.44	64.074
ALP	50	184	285	235.18	29.230
DURATION OF HAART	50	2.92	7.54	4.4030	1.0977

AGE GROUP :

Table 5.2 – Age Group Analysis with LFT

	< 40 yrs		>40 yrs		Oneway ANOVA F Test
	Mean	**SD**	**Mean**	**SD**	
TB	4.02	0.551	4.92	1.056	F =4.179,p =0.000
SGOT	314.10	44.481	356.95	34.896	F =2.050,p =0.040
SGPT	376.03	51.211	422.24	71.321	F =1.302, p =0.258
ALP	219.52	19.057	256.81	27.164	F =1.817, p =0.072

Considering Age as an independent factor for elevated liver enzymes, 2 age groups were analysed (A < 40 yrs, B >40). Though age >40 yrs showed elevated liver enzymes,There was no statistical significance difference between age and hepatotoxicity.

SEX :

Table 5.3 – Analysis of sex with LFT

	Male		Female		Oneway ANOVA F test
	Mean	**SD**	**Mean**	**SD**	
TB	4.52	1.100	4.20	0.414	F=1.495 p=0.227
SGOT	319.81	53.296	352.16	15.942	F=6.591 p=0.013
SGPT	393.94	78.328	397.89	30.663	F=0.044 p=0.835
ALP	244.32	31.899	220.26	15.846	F=9.339 p=0.004

Comparing the means of liver function tests with Sex ,sex show no statistically significant difference with hepatotoxicity.(p >0.05)

BODY MASS INDEX (BMI)

Analysis of data with BMI as an independent variable show no statistically significant difference between BMI and hepatotoxicity. (p>0.05).

Table 5.4– Analysis of BMI with LFT

	BMI				
	<18.5		**> 18.5**		
	Mean	**SD**	**Mean**	**SD**	**Oneway ANOVA F Test**
TB	4.23	0.937	4.55	0.875	F=1.566, p=0.217
SGOT	325.71	54.357	338.00	35.930	F=0.903, p=0.347
SGPT	390.33	68.908	400.15	60.250	F=0.289, p=0.593
ALP	230.92	33.060	239.12	25.210	F=0.981, p=0.327

Alcohol:

Table 5.5 – Analysis of Alcohol with LFT

	ALCOHOL				
	YES		NO		
	Mean	**SD**	**Mean**	**SD**	**One wayANOVA F Test**
TB	4.61	1.216	4.27	0.650	F=1.577 p=0.215
SGOT	335.53	51.418	330.00	42.492	F=0.170 p=0.682
SGPT	426.68	69.585	376.29	52.945	F=8.385 p=0.006
ALP	247.00	30.944	227.94	26.043	F=0.006 p=0.024

Analysing with alcohol and hepatotoxicity did not show any statistical significance difference between them. ($p > 0.05$).

CD4 COUNT:

Table 5.6 –Analyses of CD4 counts with LFT.

	< 105		>105		
	Mean	**SD**	**Mean**	**SD**	**Oneway ANOVA F test**
TB	4.65	0.878	4.13	0.880	F=4.517 p=0.039
SGOT	359.77	20.294	302.13	46.788	F=32.821 p=0.000
SGPT	421.92	55.619	366.75	61.092	F=11.175p= 0.002
ALP	242.65	31.079	227.08	25.274	F=3.889 p=0.049

The association of hepatotoxicity with different CD4 counts catagories was analyzed. Analyses show statistically significant difference between the patients belonging to CD4 count < 105and hepatotoxicity.($p < 0.05$).

HBV:

Table 5.7- Analysis of Co-infection with HBV with LFT

	HBV				Oneway ANOVA F test
	YES		NO		
	Mean	SD	Mean	SD	
TB	4.98	1.133	4.25	0.910	F=5.549 p=0.023
SGOT	372.40	22.192	322.02	45.651	F=11.910 p=0.001
SGPT	463.70	36.185	378.38	64.074	F=19.561p=0.000
ALP	259.10	28.041	229.20	29.230	F=9.890p=0.003

Coinfection with HBV increases the risk of hepatotoxicity. The data analysed show statistically significant difference between with HBV positivity& hepatotoxicity. ($p< 0.05$)

HCV:

Table 5.8 - Analysis of Co-infection with HCV with LFT

	HCV				Oneway ANOVA F test
	YES		NO		
	Mean	SD	Mean	SD	
TB	6.13	0.252	4.29	0.819	F=14.851p=0.000
SGOT	386.00	12.767	328.66	44.847	F=4.794p=0.033
SGPT	487.67	8.386	389.55	61.482	F=5.422p=0.024
ALP	271.67	5.508	232.85	28.573	F=5.422p=0.024

Coinfection with HCV increases the risk of hepatotoxicity. The data analysed show statistically significant difference between HCV positivity and hepatotoxicity.($p<0.05$).

COMBINATION OF ALCOHOL,HBV& HCV:

Table 5.9 - Analysis with combination of HBV, HCV & Alcohol with LFT.

	ALCOHOL-HBV-HCV				Oneway ANOVA F Test
	YES		NO		
	Mean	SD	Mean	SD	
TB	5.31	1.075	4.20	0.745	F=13.897p=0.001
SGOT	376.56	24.414	322.34	43.491	F=12.946p=0.001
SGPT	480.78	16.791	376.71	54.539	F=31.646p=0.000
ALP	271.56	9.235	227.20	25.817	F=25.495p=0.000

On combining HBV, HCVcoinfection and alcohol abuse there was a statistically significant difference between hepatotoxicity and HBV,HCV and alcohol abuse. ($p< 0.05$).

REGIMEN

Table 5.10 - Analysis between various Treatment Regimens(ZLN & ZLE Regimen) with LFT

	REGIMEN								Oneway Anova F Test
	ZLN		ZLE		SLN		SLE		
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
TB	4.41	1.035	3.98	0.340	4.34	0.894	4.64	0.916	F=0.549 p=0.651
SGOT	322.69	48.981	291.00	61.281	337.53	40.315	351.36	35.767	F=2.201 p=0.101
SGPT	386.13	65.207	389.00	115.761	404.11	51.097	396.36	68.701	F=0.231 p=0.874
ALP	231.13	26.066	229.75	32.725	233.63	31.261	245.73	30.365	F=0.629 p=0.600

Considering associations between various treatment regimens

REGIMEN 1 :Zidovudine + Lamivudine + Nevirapine (ZLN)

REGIMEN 2:Zidovudine + Lamivudine + Efavirenz (ZLE)

REGIMEN 3 :Stavudine + Lamivudine + Nevirapine (SLN)

REGIMEN 4: Stavudine + Lamivudine + Efavirenz (SLE) and Liver Function Test (TB,AST,ALT,ALP,).

The data were analysed by One way ANOVA F test. There was no statistical difference between different regimens in causing hepatotoxiciy. ($p > 0.05$).

Table 5.11- Analysis of Duration of HAART and LFT

	DURATION OF HAART				**Oneway Anova F Test**
	Mean	**SD**	**Mean**	**SD**	
TB	4.82	0.944	4.18	0.826	F=5.976 p=0.018
SGOT	357.41	31.853	319.06	46.563	F=9.252 p=0.004
SGPT	409.18	64.189	388.36	63.831	F=1.188 p=0.281
ALP	242.82	31.235	231.24	27.811	F=1.790 p=0.187

Comparing with duration of HAART and hepatotoxicity ,it did not show any statistical significance. ($p > 0.05$).

Table 5.12 – Analysis of Patients receiving HAART and ATT drugs with LFT

	ATT				Oneway ANOVA F test
	YES		NO		
	Mean	SD	Mean	SD	
TB	4.46	0.846	4.37	0.947	F=0.091 p=0.764
SGOT	335.27	49.819	330.74	44.443	F=0.101 p=0.752
SGPT	394.40	79.084	395.89	57.799	F=0.006 p=0.941
ALP	241.47	30.685	232.49	28.613	F=0.991 p=0.324

Comparing patients receiving HAART and ATT drugs with hepatotoxicity, show no significant difference.($p>0.05$).

Discussion

DISCUSSION

There is an increase in the reporting of drug induced liver injury following ART therapy since 1995 following wide spread usage of antiretrovirals [144] .

The incidence of drug hepatotoxicity has been variously reported. It ranged from 5% to 30% in different series (17 cohorts and 2 metaanalyses). Less often they cause steatosis, Lactic acidosis and encephalopathy with mortality rates between 0.1 to 7%.Our incidence is likely to be around 4% when grade 3 or 4 injury is taken as cut off limit.

We compared our results with that of the literature available on this issue. Much of the data came from large trials like Amsterdam, CHORUS, ICONA and TARGET which involved more than 5100 patients.[145-149]

AGE, SEX AND BMI :

Age was not considered to be an individual risk factor in most of the published series. Age has not been found consistently to be an independent risk for elevated liver enzyme values [145],[150],[151],[152]. .As Large trials like Saves[148] failed to demonstrate any correlation with age. Our series also found no correlation to the incidence of hepatotoxicity with age.

Female sex was associated with increased incidence of hepatotoxicity in two of the major trials. Martin-Carbonero[19]et al and Wit et al[147] have shown independently that female sex is an independent risk factor and the

risk increases with females who are obese and who drink alcohol. Our data found no correlation of hepatotoxicity with gender. Both sexes had equal incidence of liver injury. Obese patients had a higher risk of hepatic steatosis and liver injury (Carr A et al).

Other studies (Sampras K et al) have shown that malnutrition and low BMI are also contributory factors in hepatic injury in Asian and African populations (Sampras K et al). In our series there is a no correlation with liver injury (Bilirubin level, AST, ALT) with BMI .Most of our patients in the sample had their BMI within normal limit. Since our study population were small in number, this parameter has to be reevaluated on larger population.

DRUGS AND REGIMENS:

Previously number of reports of increased liver injury were attributed to certain drugs like Zidovudine, Nevirapine , full dose Ritonavir. Review of 17 clinical trials between 1991 to 2001 in FDA database attributes risk of liver injury for Nevirapine (NVP) and Efavirenz (EFZ).

In 2NN study, post exposure prophylaxis of NVP was associated with severe liver injury and it was recommended to exclude NVP from PEP programs. Our series included 4 standard regimen (Zidovudine + Lamivudine + Nevirapine , Zidovudine + Lamivudine + + Efavirenz, ,Stavudine + Lamivudine + Nevirapine, Stavudine + Lamivudine + Efavirenz,). When these were compared with the incidence of liver injury

there was no correlation. All regimens had equal incidence of hepatotoxicity following therapy.[153] Patients receiving both HAART and ART show no statistically significant difference with hepatotoxicity, as PI's were not included in our regimens in patients receiving ATT. Rifampicin and PI combination is associated with significant elevation of transaminases.[158]

ALCOHOL:

Alcohol usage did not predispose to severe liver injury in studies by Saves et al. [155] Sulkowski et al[154] and Rodriguez-Rosado.[144]However Nunez et al[145]found alcohol has correlation particularly following PI based regimens and in obese females (Martin –Carbonero). Our study did not find any correlation of hepatotoxicity with alcohol usage. However we found that there were significant risks associated with presence of combined factors of alcohol and HBV, HCV.

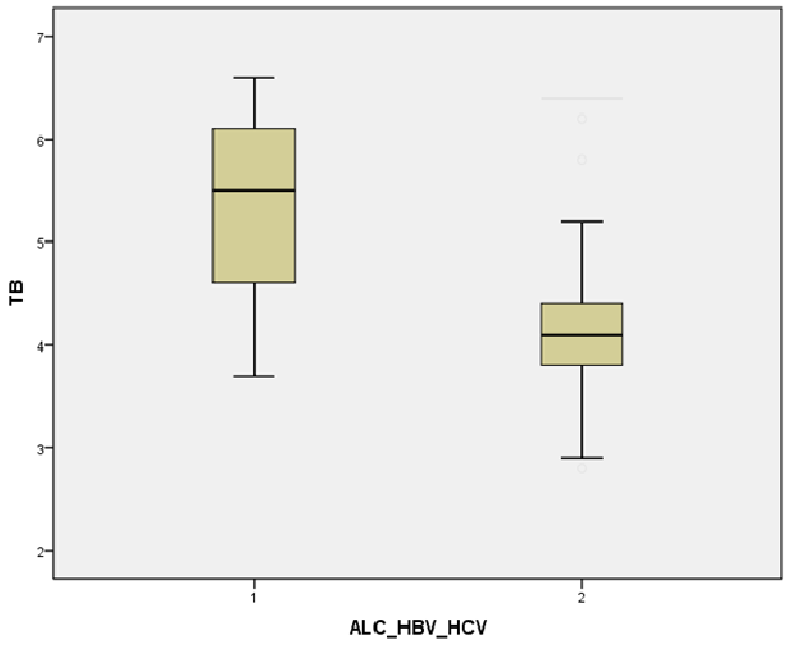

Figure 6.1 – Analyses of combination of Alcohol, HBV & HCV with LFT

HEPATITIS B AND HEPATITIS C

There are atleast 10 studies which show consistent association of liver toxicity with HBV infection. Studies by Saves, Sulkowski[154], Den Brinker, D'Armino, Aceti[156],Wit [147], DeMaat have shown that HBV is an individual risk factor. The risk increased with high viral load, HBeAg positivity and raised baseline AST and ALT. Co infection with HCV is also identified as a contributing factor in these studies. Withdrawal of Lamivudine in HBV positive patients also found to have higher incidence of hepatotoxicity.

In our patients HBV is strongly associated with increased incidence of hepatotoxicity. Ithas good correlation with Bilirubin, AST, ALT, The incidence of HBV coinfection in the study population is 20% and HCV is 6%.

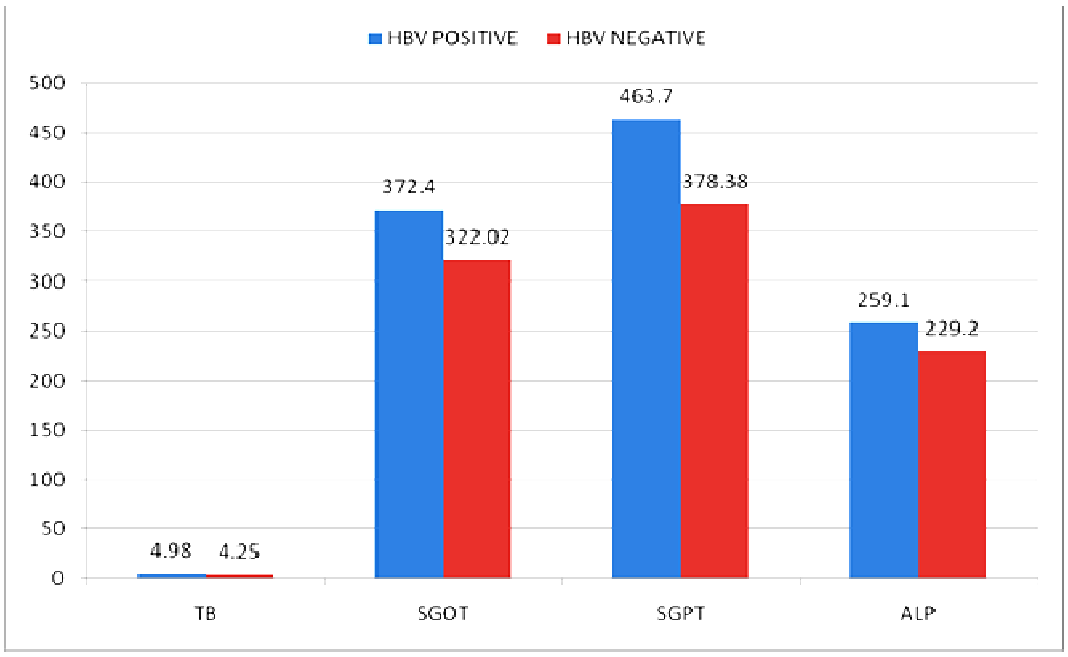

Figure 6.2 –Analysis of HBV with LFT

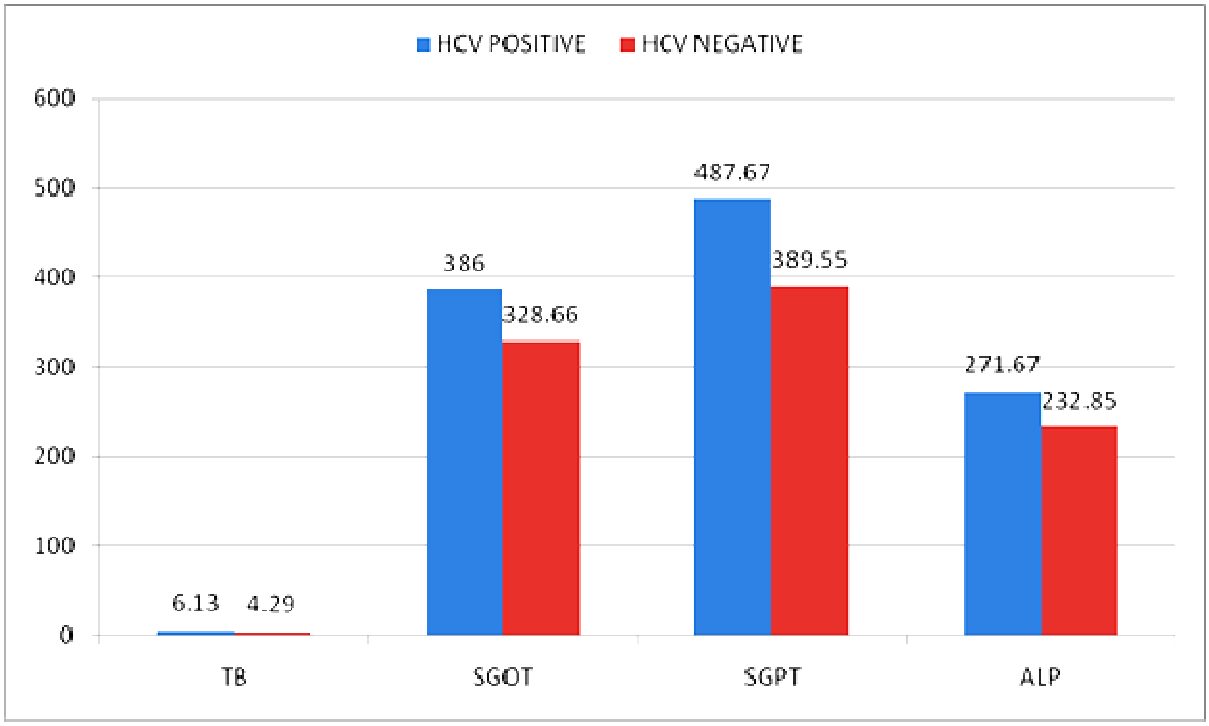

Figure 6.3 -Analysis of HCV with LFT

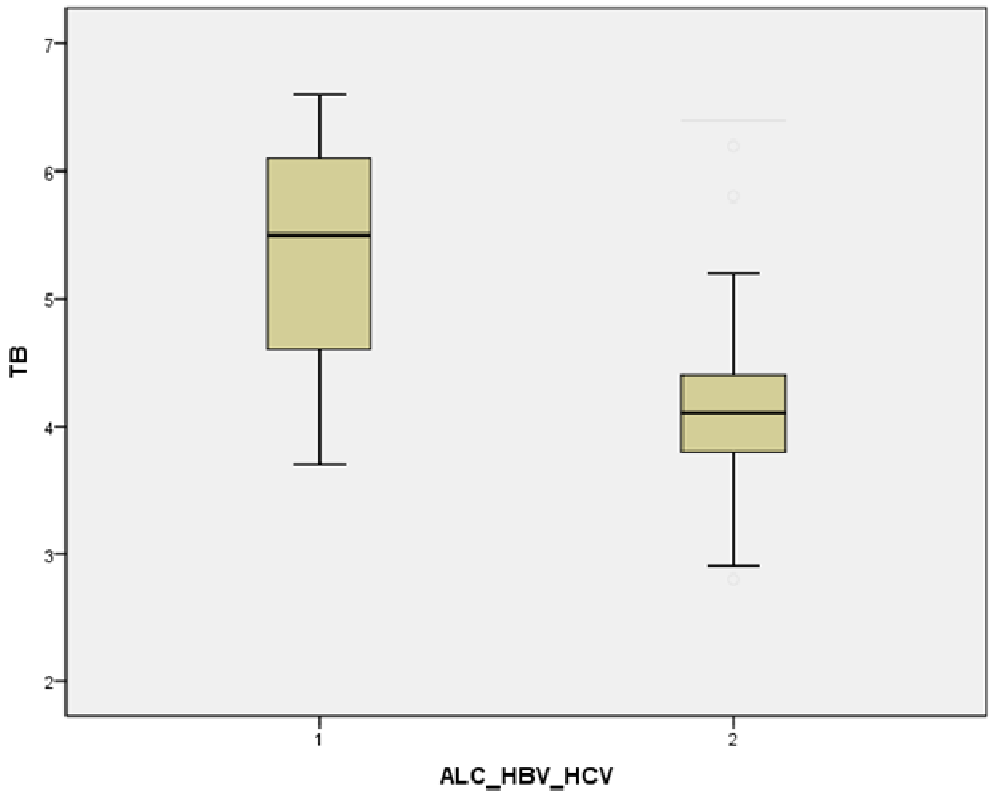

Figure 6.4 –Analyses of combination of alcohol, HBV, HCV with LFT

CD4 COUNT:

The correlation with CD4 count and hepatotoxicity was found in our study. Patients with CD4 < 105 cells ran a higher risk of hepatotoxicity and death. This is attributed to profound state of immune suppression and loss of liver regeneration functions. Studies by Saves had similar results. A study by Sulkowski[154] showed that a rise in CD4 count following HAART predisposes to severe hepatic injury. He attributes this phenomenon to immune reconstitution syndrome where restoration of cell mediated immunity caused aggressive hypersensitivity reaction to drugs. This phenomenon was also confirmed by other recentstudies.[157],[147],[155]

Most of our patients had CD4 counts moderately elevated after induction of ART and this phenomenon was not observed in our series.

Conclusion

CONCLUSIONS

The following were concluded at the end of the study

1. Drug induced liver injury occurs in 4% of patients following HAART therapy.
2. The risk factors for hepatotoxicity identified were Low CD4 count, HBV co-infection, HCV infection and combined HBV,HCV co-infection & alcohol usage.
3. Age, Sex,BMI,did not have any correlation with the incidence and severity of hepatotoxicity.
4. Similarly alcohol usage alone, various regimens, Duration of HAART did not have any correlation with the incidence and severity of hepatotoxicity.
5. Mortality rate was 2%.(Patient died of acute fulminant hepatic Failure).

Summary

SUMMARY

The study was initiated with the primary aim of finding out the clinical profile and risk factors for the hepatotoxicity in patients receiving HAART therapy for AIDS.

A total of 1250 patients were screened and patients who developed liver injury (grade 3 or 4) during ART therapy were selected. About 50 adult patients of both the sexes were included in the study. Records of these patients were analysed. Further testing was done as needed.

Various parameters were noted. Statistical analysis was done by Oneway ANOVA F test, in which correlation between various parameters and hepatotoxicity were analysed. Results were tabulated and compared with various published series worldwide.

According to our series, the major risk factors for hepatotoxicity were Hepatitis B coinfection(20%),Hepatitis C coInfection(6%), Low CD4 counts, alcohol abuse in HBV ,HCV positive patients.

The risk of liver injury was independent of age, sex, BMI, various drug combinations, Duration of HAART. These results were comparable with publishes series from various countries although subtle differences exist.

					MASTER CHART - Page 1										
S.NO	**NAME**	**AGE**	**SEX**	**BMI**	**ALCOHOL**	**CD4**	**TB**	**SGOT**	**SGPT**	**ALP**	**HBV**	**HCV**	**REGIMEN**	**OTHERS**	**DURATION**
1	AAA	47	M	18.8	NO	115	4	287	235	224	NEG	NEG	Z+L+N		9.06
2	AAB	36	F	18	NO	102	4	354	385	224	NEG	NEG	S+L+N		8.2
3	AAC	58	M	16.4	YES	90	5	390	488	285	POS	NEG	S+L+E	ATT-CAT-I	11
4	AAD	36	M	20.4	NO	126	4	259	385	220	NEG	NEG	Z+L+N		10.03
5	AAE	32	F	18.2	NO	108	3	369	380	220	NEG	NEG	Z+L+N		11.31
6	AAF	42	F	19.7	NO	118	4	357	393	217	NEG	NEG	S+L+N		10
7	AAG	33	M	16.5	NO	162	4	251	288	224	NEG	NEG	Z+L+E	ATT-CAT-I	11.23
8	AAH	36	F	25.5	NO	98	5	353	483	234	NEG	NEG	S+L+N		11.83
9	AAI	42	M	21	YES	91	4	380	499	276	POS	NEG	Z+L+E	ATT-CAT-I	12.05
10	AAJ	35	M	19.3	YES	108	4	283	479	220	NEG	NEG	Z+L+E	ATT-CAT-I	13.42
11	AAK	39	F	17.1	NO	101	4	359	394	216	NEG	NEG	S+L+E	ATT-CAT-I	11.35
12	AAL	34	M	20.5	YES	93	5	315	442	254	POS	NEG	Z+L+N		10.08
13	AAM	54	M	16.2	YES	62	6	365	485	277	NEG	NEG	S+L+E	ATT-CAT-I	13.12
14	AAN	25	M	25.7	YES	111	3	305	350	225	NEG	NEG	Z+L+N		9.75
15	AAO	35	M	17.8	YES	148	4	281	345	223	NEG	NEG	Z+L+N		8.63
16	AAP	30	M	17.8	NO	145	4	260	302	204	NEG	NEG	Z+L+N		10.04
17	AAQ	35	M	15.2	NO	138	4	250	290	199	NEG	NEG	Z+L+E	ATT-CAT-I	12.62
18	AAR	25	F	20.8	NO	90	4	350	388	226	NEG	NEG	S+L+E	ATT-CAT-I	11.07
19	AAS	27	M	16.5	NO	112	3	283	356	184	NEG	NEG	S+L+N		9.41
20	AAT	30	F	19.8	NO	76	5	366	399	196	NEG	NEG	Z+L+N		11.64
21	AAU	45	F	14.2	NO	56	4	370	405	190	POS	NEG	S+L+N		9.51
22	AAV	28	F	17.8	NO	78	4	375	455	198	NEG	NEG	Z+L+N		8.11
23	AAW	23	F	17.7	NO	89	4	352	420	218	NEG	NEG	S+L+N		10.48
24	AAX	50	M	18	NO	41	6	380	486	278	NEG	NEG	S+L+N		11
25	AAY	58	M	16.4	YES	92	6	397	493	278	NEG	POS	S+L+E	ATT-CAT-I	12.07
26	AAZ	47	M	19.5	NO	58	5	359	365	268	NEG	NEG	S+L+E	ATT-CAT-I	11.83
27	ABA	39	M	15.2	NO	126	4	261	343	264	NEG	NEG	S+L+N		10.4
28	ABB	29	F	22	NO	114	4	320	388	221	NEG	NEG	S+L+N		11.01

MASTER CHART - Page 2

S.NO	NAME	AGE	SEX	BMI	ALCOHOL	CD4	TB	SGOT	SGPT	ALP	HBV	HCV	REGIMEN	OTHERS	DURATION
29	ABC	44	M	22.7	NO	153	6	259	387	270	NEG	NEG	Z+L+N		9.95
30	ABD	52	M	19.3	YES	85	6	389	492	268	POS	POS	Z+L+N		10.38
31	ABE	32	M	21.9	YES	94	4	348	356	206	NEG	NEG	Z+L+N		8.95
32	ABF	52	M	18.5	YES	80	6	372	478	269	POS	POS	S+L+N		9.94
33	ABG	43	M	18	YES	119	4	343	384	259	NEG	NEG	S+L+N		10.08
34	ABH	35	M	14.9	YES	166	4	260	286	225	NEG	NEG	S+L+E	ATT-CAT-I	12.07
35	ABI	29	M	18	YES	150	3	274	345	195	NEG	NEG	S+L+N		8.86
36	ABJ	47	M	17.8	YES	80	4	376	475	264	POS	NEG	S+L+N		10.54
37	ABK	31	M	17.6	YES	136	4	258	350	192	NEG	NEG	S+L+N		10.26
38	ABL	45	M	19.1	NO	61	5	349	326	277	NEG	NEG	S+L+E	ATT-CAT-I	11.35
39	ABM	40	M	20.2	NO	100	4	341	342	269	NEG	NEG	S+L+N		9.01
40	ABN	46	F	22	NO	69	4	330	398	216	NEG	NEG	S+L+E	ATT-CAT-I	11.37
41	ABO	43	F	18.5	NO	83	4	320	378	223	NEG	NEG	S+L+N		9.72
42	ABP	33	M	15.9	YES	184	4	269	400	227	NEG	NEG	Z+L+N		8.95
43	ABQ	39	F	22.2	NO	115	5	333	364	228	NEG	NEG	Z+L+N		9
44	ABR	31	F	22.2	NO	98	4	360	338	219	NEG	NEG	S+L+E	ATT-CAT-I	11
45	ABS	46	M	18	YES	147	6	380	475	279	POS	NEG	S+L+N		10.34
46	ABT	30	F	22.2	NO	66	5	358	401	264	NEG	NEG	Z+L+N		8.86
47	ABU	47	F	19.5	NO	118	4	362	398	235	POS	NEG	S+L+N		8.99
48	ABV	38	F	23.7	NO	112	5	357	394	224	NEG	NEG	S+L+N		9
49	ABW	39	F	18.5	NO	99	4	346	399	216	NEG	NEG	S+L+E	ATT-CAT-I	11.38
50	ABX	54	M	21.8	YES	108	7	390	485	271	POS	NEG	Z+L+N		11.76

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